

Mild phenotype associated with an interstitial deletion of the long arm of chromosome 1

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Abstract

We report on a 21 month old child referred to us because of facial dysmorphism and psychomotor retardation. The patient's phenotype was characterised by a wide and receding forehead, broad nasal bridge, redundant retronuchal skin, low set and poorly shaped ears, micrognathia, and small hands and feet. High resolution R and G banding karyotype analysis of peripheral blood lymphocytes showed an interstitial deletion of the long arm of chromosome 1 spanning bands q22 to q24. The cytogenetic results were confirmed by molecular analysis. The phenotype observed in our patient was relatively milder than those reported in other patients with an interstitial deletion of chromosome 1q. (*J Med Genet* 1998;35:1047-1049)

Keywords: chromosome 1q; interstitial deletion; antithrombin III

Few reports of interstitial deletions of the long arm of chromosome 1 have been published.¹⁻⁶ In all cases the patients had complex phenotypes including dysmorphism, growth and developmental delay, and organ abnormalities. The deletions were characterised either by conventional cytogenetic techniques or, in more recent reports, by fluorescent in situ hybridisation (FISH).

Here we report on a 21 month old child presenting with a relatively mild phenotype characterised by mild facial dysmorphism, mild psychomotor delay, and hypotonia. Karyotype analysis showed an interstitial deletion of the long arm of chromosome 1 spanning 1q22 to q24. The cytogenetic data were confirmed by molecular analysis.

Case report

The proband, a male, was the first child of healthy Italian parents. The family history was negative for repeated abortions, stillbirths, congenital malformations, or mental retardation. His father was 45 and his mother was 31 years old. The pregnancy was uncomplicated; ultrasonography and karyotyping of amniotic fluid cells were performed during pregnancy and were reported to be normal. Spontaneous vertex delivery occurred at 41 weeks of gestation. Birth weight was 3530 g, length 51 cm, and occipitofrontal circumference (OFC) 35 cm.

At 2 days of age, he was admitted to a neonatal care unit because of respiratory distress. Physical examination showed dysmor-

phic features including a wide and receding forehead, broad nasal bridge, redundant retronuchal skin, low set and poorly shaped ears, and micrognathia. Skull asymmetry and dolichocephaly were also present.

The patient was admitted to our Department at the age of 21 months. At that time, clinical examination showed weight between the 50th and 75th centile, height between the 10th and 25th centile, and OFC between the 25th and 50th centile. Facial dysmorphism was present, with a broad nasal bridge, redundant retronuchal skin, and low set, poorly shaped ears (fig 1). Neurological examination showed mild psychomotor delay and hypotonia. Small hands (total length 9 cm, 3rd centile; palm length 5 cm, below the 3rd centile) and feet (total length 12 cm, below the 3rd centile) were observed. Routine biochemical analyses were in the normal range. Antithrombin III (ATIII) levels were 23 mg/dl (normal values 30.8±9.4 mg/dl).

An x ray of the hands showed delayed bone age (9-11 months). Transfontanelle cranial ultrasonography was normal. A patent foramen ovale was detected by echocardiography.

Material and methods

CELL CULTURES AND CYTOGENETIC ANALYSIS

R and G banding karyotype analyses were performed according to published procedures.⁷ A cell line has been established and is available.

MOLECULAR ANALYSIS

Genomic DNA was isolated from peripheral blood samples by standard methods.⁸ Three microsatellite markers of chromosome 1q were analysed, D1S104, D1S1167, and D1S158, located in 1q21-23, 1q21.3-q23.2, and 1q24-pter, respectively. PCR amplification of D1S104 (GDB 177300), D1S1167 (GDB 309963), and D1S158 (GDB 182041) was performed in a DNA thermal cycler 480 (Per-



Figure 1 The proband at the age of 21 months.

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Received 23 January 1998
Revised version accepted for publication 6 May 1998

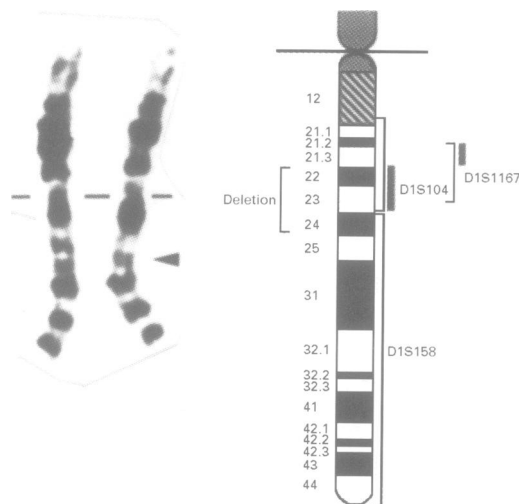


Figure 2 High resolution G banding of chromosome 1q in the proband (550 bands approximately). A schematic representation of chromosome 1q is provided, showing the deleted segment. The boxes indicate the positions of the microsatellite markers shown by molecular and cytogenetic analysis. The arrow indicates the interstitial deletion.

kin Elmer, Branchburg, NJ, USA) using 25 ng genomic DNA as template, 100 ng of each primer, 250 $\mu\text{mol/l}$ dNTPs, 1 \times PCR buffer (Gibco, Paisley, UK), 0.4 μl ^{32}P -dCTP, and 2.5 U *Taq* polymerase (Gibco, Paisley, UK) in a 25 μl final volume. The concentrations of MgCl_2 were 2 mmol/l, 1.5 mmol/l, and 1.75 mmol/l, respectively. In all cases, initial denaturation at 94°C (seven minutes) was followed by 39 cycles of denaturation at 94°C (one minute), annealing at 55°C (one minute), and extension at 72°C (one minute). The PCR products were separated on a standard 6% denaturing polyacrylamide gel and, after electrophoresis, bands were visualised by autoradiography after two days of exposure to Kodak x ray films (Eastman Kodak Company, Rochester, NY, USA).

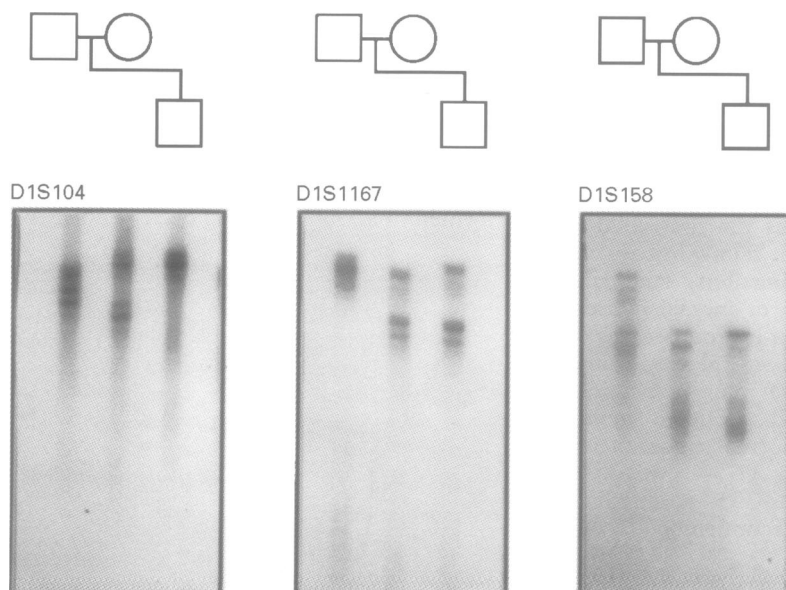


Figure 3 Molecular analysis of the proband and his parents. Only the D1S104 paternal allele was deleted in the proband.

Results

CYTOGENETIC ANALYSIS

R and G banding karyotype analyses showed a microdeletion of the long arm of chromosome 1, 46,XY,del(1)(q22q24) (fig 2). The parents' karyotypes were normal.

MOLECULAR ANALYSIS

Microsatellite analysis was informative for all the markers used in the present study. Haploinsufficiency for the D1S104 marker only was found and determined to be of paternal origin. No haploinsufficiency was detected in the parents' DNA (fig 3).

Discussion

We have found an interstitial deletion spanning chromosome 1q22 to q24 in a 21 month old boy by using both cytogenetic and molecular techniques. The three microsatellites studied (D1S104, D1S1167, and D1S158) were informative and only D1S104 appeared to be deleted in the patient. The molecular analysis allowed the identification of the paternal origin of the deleted chromosome 1. Moreover, the molecular data, taken together with the cytogenetic results, suggested that the localisation of D1S104 should be restricted to 1q22-q23 and that of D1S1167 should be restricted to 1q21.3-q22. The normal ATIII levels observed in our patient confirm the localisation of the ATIII locus, previously assigned to the 1q24-q25.1 region.^{6, 10}

Interstitial deletions of the long arm of chromosome 1 have previously been described. Three distinct clinical pictures, resulting from 1q21-q25, 1q25-q32, and 1q42-qter monosomies, respectively, were recognised.² Patients with chromosome 1q21-q25 deletion, which overlaps the deletion observed in our patient, had a severe phenotype, including pre- and postnatal growth deficiency, psychomotor retardation, and facial dysmorphism, such as microphthalmia, short and bulbous nose, cleft lip and palate, oligodontia, poorly modelled auricles, and small hands and feet with short fingers and toes. X ray examination of these patients showed multiple phalangeal abnormalities and absence of the 12th rib. Severe congenital heart disease and kidney hypoplasia have also been described.^{1, 3}

In contrast, our patient had a relatively mild phenotype, with minor facial dysmorphism and mild psychomotor delay. The mild phenotype observed in our patient could be explained as being the result of a smaller deletion.

A careful clinical analysis of patients with chromosomal aberrations could establish phenotype-genotype correlations and could be of help in mapping candidate loci of human disease genes.

We are grateful to Dr G Sebastio for the critical reading of the manuscript and for helpful discussion.

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